REMARKS

Claims 12-25 are pending in the application. Claims 1-11 and 26-46 are withdrawn from consideration. Claim 12 has been amended and claims 19 and 22 have been cancelled.

Applicants submit herewith certified copies of JP 2000-115091 and JP 2000-203850 and a Request for Continued Examination (RCE) under 37 C.F.R. 1.114.

Applicants wish to thank Supervisory Patent Examiner Wilson and Examiner Lewis for granting and participating in a telephone interview on June 19, 2003.

Applicants have inserted the term "protein" directly before each recitation of the term "drug" in claim 12. Claim 12 as amended is now directed to a method for preparing sustained release protein drug compositions. Pursuant to suggestions made by Examiners Wilson and Lewis in the telephone interview, Applicants have also replaced the term "level sufficient" with the term "pH of about 3" in claim 12. Support for these amendments can be found in the specification, e.g., at page 2, lines 2, 9-15, and 22-24 and in claims 12, 19, and 20 as originally filed.

The Examiner has maintained the rejection of claims 12-26 under 35 U.S.C. 103(a) as being unpatentable over Suzuki et al, EP 0 913 149 A1 (Suzuki) in view of Igari et al., U.S. 5,344,644 (Igari).

Applicants do not agree with the rejection. However, in order to expedite prosecution, Applicants have amended claim 12 to limit the drug to a "protein drug" and the precipitating pH to a "pH of about 3."

Claim 12 as amended and its dependent claims are directed to a method of producing sustained release drug compositions in which the drug is a protein drug. Briefly, lowering the pH of a precipitating solution containing the protein drug, a mucopolysaccharide and carrier protein precipitates the compositions. Our specification specifically teaches that the pH is lowered to about 3 using aqueous hydrochloric acid (see, e.g., Examples 2 and 3, page 7, line 16 through page 8, line 15 and Examples 8, 9 and 10, page 9 line 21 through page 11 line 6).

The compositions obtained by the claimed method exhibit sustained protein drug release rates that are unexpectedly superior to those of known sustained release drug compositions (see, e.g., the above-mentioned examples and Figures 6, 8, and 9). These data show that compositions made by the claimed method release the drug component over extended time periods, e.g., seven

days, whereas compositions prepared by methods currently available in the art release the drug component over much shorter periods of time, e.g., twenty-four hours. Further, these compositions release the protein drug in active form (see, e.g., Examples 9 and 10). In other words, the protein drug that is released from the drug composition precipitated at pH 3 is not structurally or functionally compromised.

Suzuki discloses adjusting the pH of preparatory solutions with very dilute acetic acid (e.g., 1% aqueous solutions, Suzuki, page 5, lines 25-26) to dissolve certain "ingredient (a)" components. Igari describes the preparation of active peptide drug compositions at pH 4-8, preferably 5-8 (Igari, column 6, line 50-52). The recitation of the preferred pH range in Igari is prefaced with the following caveat:

> The pH of a solution prepared from the water-soluble composition of the present invention should be such that said pH will not exert any adverse influence upon the activity of the pharmacologically active peptide...(Igari, column 6, lines 43-46).

One of skill in the art would recognize that a pharmacologically active peptide can, e.g., denature at acidic pH and would understand this statement to mean that when preparing an active peptide drug compositions, a pH of 4-8 should be employed. Clearly, the art of record does not suggest that sustained release protein drug compositions could be advantageously produced at a pH less than 4. Thus, at the time the invention was made, it would not have been expected that a protein drug would be successfully reproduced and sustained released in an active form from a composition obtained by precipitating an active protein drug at a pH below 4.

In view of the above, the claimed method of preparing sustained release protein drug compositions, i.e., generating and precipitating the protein drug compositions at pH 3, is contrary to accepted wisdom in the art. Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness (MPEP, section 2145, part X, D.3, page 2161). Reference is made to the findings of *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986):

> PTO acted erroneously in determining that claimed process for sulfonating diphenol sulfone at its molten state would be obvious from prior art, since references all suggest that lower temperatures are preferable, and none suggests

> that reaction may be advantageously produced at molten state, and since data produced by the inventor, and not challenged by PTO, show significant advantages of claimed invention, so that, on balance, inventor proceeded contrary to accepted wisdom, which is strong evidence of unobviousness (*In re Hedges*, 228 USPQ 685, part 1).

Thus, it would not have been obvious to prepare sustained release drug compositions containing protein drugs via precipitation at pH 3 because these operating conditions are contrary to the wisdom in the art, which teaches that active proteins can be denatured, and therefore rendered inactive, at this pH.

Applicants submit that independent claim 12 (as amended) is obvious over Suzuki in view of Igari for the reasons stated above. Since claims 13-25 depend from claim 12, these claims also are not rendered obvious by Suzuki and Igari. Applicants therefore respectfully request that the rejection of claims 12-25 be withdrawn.